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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,653	EISENBACH-SCHWARTZ ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-13,15 and 17-49* is/are pending in the application.

4a) Of the above claim(s) *21,26-30,35 and 40-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-13,15,17-20,22-25,31-34,36-39 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-5,7,9-13,15 and 17-49* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 17 September 2007 has been entered in full. Claims 1-3, 9-11, 18, 21-23, 26-28, 30, 36-45, and 47 are amended. Claims 6, 8, 14, 16, and 50-51 are cancelled.

Election/Restrictions

At page 12 of the Response of 17 September 2007, Applicant affirms that a telephone election was made on November 22, 2006 to examine the species of myelin basic protein. Applicant now argues that this election was made in error. Applicant has now advised that the preferred species for initial examination is the Nogo-A peptide. Applicant requests that the examiner permit a shift in election, under the circumstances. Applicant submits that this should not be an inordinate hardship on the examiner as no prior was found to the elected species. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed in the previous Office Action of 16 April 2007, the species are independent or distinct because each of the antigens listed as (a)-(n) have different structural and functional characteristics. The species are independent or distinct because each requires separate, non-coextensive searches. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

The requirement is still deemed proper and is therefore made FINAL.

Claims 21, 26-30, 35, 40-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 17 September 2007.

Claims 1-5, 7, 9-13, 15, 17-20, 22-25, 31-34, 36-39, 45-49 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejection of claims 1-5, 7, 9-13, 15, 17-20, 22-25, 31-34, 36-39, and 45-51 under provisional obviousness-type double patenting as set forth at pages 12-13 of the previous Office Action of 16 April 2007 is *withdrawn* in view of the amended claims (17 September 2007).

Specification

2. The abstract of the disclosure is objected to because the legal term "said" is used.

Applicant is reminded of the proper language and format for an abstract of the disclosure. Correction is required. See MPEP § 608.01(b). The basis for this objection is set forth at page 4 of the previous Office Action (16 April 2007).

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 7, 9-13, 15, 17-20, 22-25, 31-34, 36-39, 45-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **(I)** a method for

reducing secondary neuronal degeneration or a method for ameliorating the secondary neurodegenerative effects that follow neuronal damage caused by an injury, disease, disorder or condition in the CNS or PNS comprising administering to an individual myelin basic protein (MBP), p51-70 of MBP, or T cells activated against MBP or p51-70, thereby reducing secondary neuronal degeneration at the injury site, *does not reasonably provide enablement for* a method for reducing secondary neuronal degeneration in the CNS or PNS comprising administering to an individual an effective amount of (i) an NS-specific antigen or an immunogenic epitope thereof, in such a manner that T cells become activated against the NS-specific antigen or administering an effective amount of T cells that are activated against said NS-specific antigen or said immunogenic thereof.

The specification is also enabling for **(II)** a method for reducing secondary neuronal degeneration or a method for ameliorating the secondary neurodegenerative effects that follow neuronal damage caused by an injury in the CNS or PNS comprising administering to an individual NogoA p472 (SEQ ID NO: 19) peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for claims 1-5, 7, 9-13, 15, 17-20, 22-25, 31-34, 36-39, and 45-51 at pages 4-9 of the previous Office Action (16 April 2007).

Applicant's arguments (17 September 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 14 of the Response of 17 September 2007, Applicant asserts that the claims have been amended to recite administration of NS-specific antigens or immunogenic epitopes thereof,

or T cells sensitized therewith. Applicant argues that information present in the specification, combined with the additional evidence that is of record in this case as to other NS-specific antigens that have been shown to be operable in the present, establish that it would not take undue experimentation to find other NS-specific antigens that would be operable for the purpose of the present invention. At page 15 of the response, Applicant states that the present invention is not based on any activity of the peptides, on the disease, but is based on the concept that if activated T-cells can be caused to accumulate at the site of neuronal degeneration, secondary neuronal degeneration will be ameliorated or reduced. Applicant indicates that in the interview on July 14, 2004, it was explained and shown with a myriad of prestigious publications from the laboratory of the present inventors, that the mere presence of these activated T-cells at the site of secondary neuronal degeneration causes a cytokine response that has a significant effect in reducing the secondary neuronal degeneration. When an NS-specific antigen is administered, which antigen is one that is present at the site of secondary neuronal degeneration, this will cause endogenous T-cells to become activated thereby and those T-cells will accumulate at the site of the secondary neuronal degeneration because of the presence at this site of the peptide with which it has been activated.

Applicant's arguments have been fully considered but are not found to be persuasive. Undue experimentation would still be required of the skilled artisan to determine what other NS-specific antigens or immunogenic epitopes of those antigens could be used to activate T cells and reduce secondary neuronal or ameliorate the effects of an injury or disease that causes secondary neuronal degeneration. As discussed in the previous Office Action, relevant literature teaches that about 200,000 distinct mRNA sequences are thought to be expressed in the brain alone (a

component of the central nervous system) and that this diversity results from the greater number and variety of cell types in the brain as compared to cells in the more homogeneous body tissues (pg 49, ¶ 1; Schwartz, J., "Synthesis and Trafficking of Neuronal Proteins", Principles of Neural Science, Connecticut: Appleton and Lange, 1991, pages 49-65). Schwartz states that the three membrane systems which constitute separate compartments within the neuron are made up of different proteins and serve separate functions within the cell (pg 50). Schwartz also continues to explain that a nerve cell makes three general classes of proteins: cystolic, nuclear/mitochondrial/peroxisomal, and cell membrane/secretory (pg 50-55). Post-filing date literature also reiterates that the central nervous system alone expresses a large and divergent proteome, comprising thousands of unique proteins (see for example, Yu et al., Molec Cellul Proteomics 3: 896-907, 2004). Therefore, due to the large quantity of proteins/antigens present in the central nervous system alone, the present invention is also unpredictable and complex wherein one skilled in the art may not necessarily reduce secondary neuronal degeneration in the central nervous system or ameliorate the effects of injury or disease that causes secondary neuronal degeneration comprising administering all possible NS-specific antigens, immunogenic epitopes thereto, or T cells activated against all possible NS-specific antigens or immunogenic epitopes thereto. Since the specification also provides no guidance regarding what immunogenic epitopes of the NS-specific antigen should be utilized for the desired activity, the skilled artisan must resort to trial and error experimentation to determine which class of compounds might yield one with the desired activity.

(ii) At page 16 of the Response, Applicant asserts that there is no reason to believe that any of these NS-specific peptides will not be operable for the purpose of the present invention, so long as they exist at the site of the secondary neuronal degeneration, as their only purpose is to activate T-cells that will then accumulate at the site of that peptide, so as to cause a cytokine response that has a significant effect in reducing the secondary neuronal degeneration.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application does not teach the reduction or inhibition of secondary neuronal degeneration by administration of any nervous system-specific antigens, other than Nogo p472, myelin basic protein (MBP), p51-70 of MBP, or T cells activated against MBP or p51-70. The specification also does not teach that all possible immunogenic epitopes derived from all possible NS-specific antigens (or activated T cells thereto) are able to reduce secondary neuronal degeneration in the central nervous system or peripheral nervous system of an individual. Undue experimentation would be required of the skilled artisan to generate peptides to all possible NS-specific antigens (and activated T cells thereto) present at the site of secondary neuronal degeneration and administer each of these peptides (or cells) to an individual to achieve the desired result of reducing secondary neuronal degeneration. Since the specification also provides no guidance regarding what immunogenic epitopes should be utilized for the desired activity, the skilled artisan must resort to trial and error experimentation to determine which peptides might yield one with the desired activity. Such trial and error experimentation is considered undue. For example, the Examiner has interpreted the administration of Nogo-A p472 (SEQ ID NO: 19) to be a critical feature of the claimed method since relevant literature teaches that other Nogo-A derived peptides possess growth-cone-

collapsing activity and inhibit neurite outgrowth (for example, GrandPre et al. Nature 403: 439-444, 2000; see pg 442, Figures 4-5).

(iii) At the bottom of page 16 of the Response of 17 September 2007, Applicant contends that the examiner has not explained why it would take undue experimentation to determine whether any given NS-specific peptide may be present at the site of secondary neuronal degeneration. Applicant explains that this is not trial and error experimentation, but can be accomplished in a systematic way, in a manner in which scientists are accustomed. Applicant submits that a wide range of diverse NS-specific antigens have been shown to be operable to cause T-cells to accumulate at the site of secondary neuronal degeneration (such as MOG, PLP, IRPB, T cells against Nogo-A). Applicant argues that this evidence serves as a "proof of concept" and is sufficient to establish the operability in a sufficient number of species to establish the possession of the genus. Applicant concludes that it would not take undue experimentation to establish the operability of the entire scope of the present claims. Applicant adds that once it is established that a particular NS-specific peptide resides in the location of the secondary neuronal degeneration, it would not take undue experimentation to determine which epitopes thereof serve to activate T cells against the peptide.

Applicant's arguments have been fully considered but are not found to be persuasive. Regarding Applicant's arguments that determining a NS-specific peptide at the site of secondary neuronal generation can be accomplished in a systematic way and that it would not take undue experimentation to determine which epitopes serve to activate T cells against the peptide, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record

once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement. See *In re Knowlton*, 500 F.2d at 572, 183 USPQ at 37; *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). As discussed above, the specification of the instant application does not teach the reduction or inhibition of secondary neuronal degeneration by administration of any nervous system-specific antigens, other than Nogo p472, myelin basic protein (MBP), p51-70 of MBP, or T cells activated against MBP or p51-70. Undue experimentation would be required of the skilled artisan to identify and generate peptides to all possible NS-specific antigens and immunogenic epitopes thereof (and activated T cells thereto) present at the site of secondary neuronal degeneration and administer each of these peptides (or cells) to an individual to achieve the desired result of reducing secondary neuronal degeneration. The specification of the instant application and Applicant's arguments have not provided any methods or evidence indicating how one skilled in the art can identify NS-specific antigens and immunogenic epitopes thereof that are present at the site of secondary neuronal degeneration. It is noted that Applicant's broad brush assertions do not constitute adequate guidance to practice the claimed method, but rather constitute an invitation to experiment empirally to determine how to practice the suggested method to obtain the therapeutic results required by the claims.

Furthermore, the post-filing date publication of Fisher et al. (J Neurosci 21: 136-142, 2001) relied upon by Applicant in the chart submitted 02 March 2006, utilizes mouse optic nerve

crush to examine immune neuroprotection with myelin-associated peptides. Specifically, Fisher et al. disclose that active immunization with the encephalitogenic peptide, PLP 139-151, leads to neuroprotection only in cases in which induced EAE is mild and that immunization has no beneficial effect in mice that develop severe EAE (page 137, column 2, first full paragraph). Fisher et al. also teach that immunization with nonencephalitogenic peptides, PLP 190-209 or MOG 1-22, lead to neuroprotection (page 137, column 1, first full paragraph; page 138; page 140, column 2). Thus, it is clear from Fisher et al. that it is not predictable which antigens or immunogenic epitopes thereof (and activated T cells) will achieve the desired result of the instant claims, i.e., reduction of secondary neuronal degeneration. Undue experimentation is required of the skilled artisan to identify the specific antigens and epitopes thereof at the site of secondary neuronal degeneration and then administer the identified antigens and epitopes thereof (or activated T cells) to reduce secondary neuronal degeneration.

Proper analysis of the Wands factors was provided in the Office Action. Due to the large quantity of experimentation necessary to identify all possible NS-specific antigens and immunogenic epitopes thereof (or activated T cells thereto) and then reduce secondary neuronal degeneration by administration of any of the above; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the unpredictability of the effects of administering any NS-specific antigen or NS-specific T cells to an individual, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

4. Claims 1-5, 7, 9-13, 15, 17, 18, 22, 23, 31, 36, 37, 45-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth for claims 1-5, 7, 9-13, 15, 17, 18, 22, 23, 31, 36, 37, 45-51 at pages 9-12of the previous Office Action (16 April 2007).

The claims are directed to a method for reducing secondary neuronal degeneration that follows neuronal damage caused by an injury, disease, or disorder or condition in the CNS or PNS comprising administering to an individual an effective amount of (i) an NS-specific antigen or an immunogenic or epitope thereof or (ii) T cells that are activated against said NS-specific antigen or said immunogenic epitope thereof.

Applicant's arguments (17 September 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant indicates that the claims have now been amended to exclude cryptic epitopes and modified epitopes. Applicant indicates that it is not understood why the Examiner takes the position that applicant has not conceived and cannot envision NS-specific antigens that are useful. At page 19 of the Response, Applicant submits that the specification conceives a long list of such antigens, the sequences all of which were known to the art at the time the present application was filed. Applicant points out that the examiner has cited evidence that the art is well aware of myriads of NS-specific peptides. Applicant states that all one has to do for the purpose of the present invention is determine whether any given peptide is present at the site of

neuronal damage. Applicant argues that the present invention is directed to the discovery that activation of T-cells with NS-specific antigens that exist at the site of secondary neuronal degeneration will cause T-cells activated thereagainst to accumulate at the site of the secondary neuronal degeneration and cause a release of cytokines that will, in turn, cause the secondary neuronal degeneration to be reduced. At page 20 of the Response, Applicant submits that there is adequate written description of this conception. Applicant argues that one of ordinary skill in the art would understand that the present inventors were in possession of the full scope of the presently claimed invention at the time the application was filed.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that the instant specification lists several examples of NS-specific antigens (page 9, [0024]). However, the specification also discloses that the definition for NS-specific antigen also includes analogs of said NS-specific antigens as described in the section on NS-specific antigens, analogs thereof, peptides derived therefrom and analogs and derivatives thereof of said peptides hereinafter (page 9, [0024]; page 41, [0100]). Thus, the skilled artisan cannot envision the NS-specific antigens or immunogenic epitopes thereof (or T cells activated against the above) of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. One skilled in the art could not envision the detailed chemical structure of all or a significant number of encompassed NS-specific antigens or immunogenic epitopes thereof, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required.

Furthermore, Applicant's broad brush argument that all one has to do for the purpose of the present invention is determine whether any given peptide is present at the site of neuronal damage does not constitute a disclosure of a representative number of NS-specific antigens or immunogenic epitopes thereof. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a recitation that the NS-specific antigen is present at the site of secondary neuronal degeneration. Additionally, there is no identification of any particular portion of the immunogenic epitope that must be conserved in order to conserve the required function. Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
21 November 2007

/Bridget E Bunner/
Primary Examiner, Art Unit 1647